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Stress Doppler Echocardiography in Systemic Sclerosis

Evidence for a Role in the Prediction of Pulmonary Hypertension

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Objective. **Patients with systemic sclerosis (SSc) in whom pulmonary hypertension (PH) is not suspected have been reported to develop an inappropriate increase of pulmonary artery systolic pressure as estimated by Doppler echocardiography under conditions of exercise (pulmonary artery systolic pressure under exercise). We undertook this study to investigate whether this increase or any other parameter detectable by stress Doppler echocardiography has utility in predicting the development of PH in SSc.**

Methods. **We enrolled a total of 170 patients with SSc previously investigated using standard and stress Doppler echocardiography and tissue Doppler imaging. Each patient was evaluated at baseline and yearly for skin and internal organ involvement. Right-sided heart catheterization was carried out when PH was suspected. The baseline Cochin Risk Prediction Score was calculated retrospectively.**

Results. **During followup, 6 patients (3.5%) developed PH. Compared with patients without any feature suggesting PH, the Cochin Risk Prediction Score was higher in this group (mean ± SD 4.2 ± 0.9 versus 3.4 ± 0.9; $P < 0.05$), as was the difference between pulmonary artery systolic pressure under exercise and pulmonary artery systolic pressure (Δpulmonary artery systolic pressure) (18.2 ± 7 mm Hg versus 9.4 ± 6.5 mm Hg; $P < 0.001$), even when adjusted for cardiac index changes. In multivariate analysis, Δpulmonary artery systolic pressure (hazard ratio [HR] 3.4 [95% confidence interval 1.4–8], $P < 0.01$) and Cochin Risk Prediction Score within the fifth quintile of the values registered in our series (HR 9.3 [95% confidence interval 1.4–63.7], $P < 0.05$) were the only factors independently predictive of PH during followup. A Δpulmonary artery systolic pressure cutoff of >18 mm Hg, identified by receiver operating characteristic curve analysis, had a sensitivity of 50% and a specificity of 90% for the development of PH during followup.**

Conclusion. **An inappropriate response to exercise among patients with SSC is detectable by stress Doppler echocardiography. Independently of other clinical associations, increased Δpulmonary artery systolic pressure heralds PH. Stress Doppler echocardiography may represent an additional screening tool for this severe complication.**

Early detection of pulmonary hypertension (PH) is critical to ensure that patients promptly receive the correct treatment for this severe pathophysiologic condition (1). Systemic sclerosis (SSc) is a connective tissue disorder whose natural course and prognosis are affected by this pulmonary vascular complication (2), which is indeed one of the most frequent causes of death in SSc patients (3). Many forms of PH, as defined by a mean pulmonary artery pressure (PAP) ≥25 mm Hg at rest (1), can occur in SSc (4,5). Precapillary PH is the most common condition (2,6), with group 1 pulmonary arterial hypertension (PAH) (1) being relatively more frequent than PH due to lung disease (group 3 PH [1]) or postembolic PH (group 4 PH [1]) (5). More rarely,

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postcapillary PH affects patients with left heart involvement (2).

Prompt diagnosis and classification based on hemodynamic features is crucial to improve outcomes and to identify patients who would benefit from specific therapies, which can dramatically change the prognosis, especially in patients with PAH (7). Unfortunately, early recognition of PH is still a largely unmet need in SSc. Indeed, only a minority of patients are diagnosed in lower New York Heart Association (NYHA) (8) functional classes or before hemodynamic parameters are severely compromised (9). Exercise stress tests have been used to screen patients in the attempt to identify early-stage PH (10–12).

We recently identified a bimodal distribution of echocardiography-estimated pulmonary artery systolic pressure under exercise in patients with SSc. In fact, we detected an inappropriate increase in pulmonary artery systolic pressure (i.e., a value ≥48 mm Hg under exercise) in ~13% of 172 patients in NYHA classes I–II who had no clinical sign or symptom of PH at study enrollment (12).

The aims of the present study were to evaluate whether an inappropriate response to exercise, or any other parameter detected during the exercise test, can predict the development of PH, and to compare the performance of the parameter(s) identified with that of the recently described Cochin Risk Prediction Score, which consists of simple clinical observations (age, forced vital capacity [FVC], and diffusing capacity for carbon monoxide/alveolar volume [DLCO/VA]) and is reported to be predictive of PH in SSc if it exceeds 2.73 (13,14).

PATIENTS AND METHODS

Patients. SSc patients consecutively attending 2 university rheumatology units were enrolled. Written informed consent was obtained from each patient, and the study was approved by the local ethics committees. The features of these patients are reported elsewhere (12). Inclusion in the study required patients to be in NYHA class I or II and to have a peak velocity of tricuspid regurgitation (VTR) of ≤3 meters/second on standard echocardiography. Patients already diagnosed as having any form of PH were excluded. The clinical characterization of patients at baseline and during followup was performed according to the European League Against Rheumatism Scleroderma Trial and Research Recommendations (15).

The following clinical and functional parameters were considered: time of onset of Raynaud's phenomenon and first non–Raynaud's phenomenon symptom, extent of skin involvement (limited cutaneous or diffuse cutaneous) according to the classification system of LeRoy et al (16), autoantibody subset, worsening of vascular manifestation or skin involvement in the last month, gastrointestinal symptoms (esophageal, stomach, intestinal), and dyspnea and its NYHA class. Interstitial lung disease (ILD) was diagnosed if FVC was <70% of the predicted value or if features of bibasilar ground-glass or reticular images were detected by high-resolution computed tomography (HRCT) of the lung irrespective of its quantification. Lung HRCT was performed if SSc was newly diagnosed at the time of inclusion in the study or if pulmonary function testing suggested ILD. Each patient was investigated at baseline and yearly for skin and organ involvement. The baseline Cochin Risk Prediction Score was calculated retrospectively using the following formula: $[0.0001107 \times \text{age}] + [0.0207818 \times (100 - \text{FVC})] + [0.04905 \times (150 - \text{DLCO/VA})]$ (13).

During longitudinal analysis, patients were referred for right-sided heart catheterization (RHC) if, at the followup visit, any sign or electrocardiogram findings suggestive of PH were detected or if the estimated systolic PAP was ≥40 mm Hg on followup echocardiography, or if DLCO was <55% of the predicted value in association with an FVC >70% of the predicted value (4). Physicians caring for the patients were blinded with regard to stress echocardiography results including pulmonary artery systolic pressure under exercise. On RHC, PH was defined as mean PAP ≥25 mm Hg and, on the basis of other hemodynamic parameters, was subgrouped according to current guidelines (1).

Echocardiography at rest and under exercise. Basal and stress echocardiography and tissue Doppler imaging were performed at both centers as previously described (12). Briefly, pulmonary artery systolic pressure was calculated by adding a right atrial pressure estimate to the peak VTR (right atrial pressure estimate was always considered 5 mm Hg both at baseline and during followup studies). Left ventricular (LV) peak early (E′) and late (A′) diastolic velocities were measured using tissue Doppler imaging at the level of the lateral mitral annulus. Cardiac index (CI) changes were recorded during exercise to adjust the increase in pulmonary artery systolic pressure (Δpulmonary artery systolic pressure/ΔCI). Doppler-estimated cardiac output was derived from the Doppler-estimated stroke volume using the velocity time integral of flow through the LV outflow tract, the diameter of the LV outflow tract, and the heart rate recorded during the imaging study. All data were analyzed by 2 observers (SG and MD) who were blinded with regard to patient data.

Statistical analysis. Continuous and categorical variables were collected and analyzed with Microsoft Excel and Stata software. Continuous variables are expressed as the mean ± SD or the median (interquartile range [IQR]) according to distribution. Categorical data are expressed as absolute and relative frequencies (numbers and percentages). Differences between groups were tested with parametric tests (for normally distributed variables), nonparametric tests (for non-normally distributed variables), univariate tests, and multivariate tests, as appropriate. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) method were applied to estimate sensitivity and specificity at different cutoffs to detect PH. Overall accuracy was measured by the AUC and reported with 95% confidence intervals. Survival was evaluated with Kaplan-Meier curves, and differences between groups were tested with the log rank method. The primary outcome for investigation was PH development. Observation

Table 1. Clinical features of the patients according to the 2 major subsets of SSc*

	Total (n = 170)	lcSSc (n = 138)	dcSSc (n = 32)	*P*
Age, mean ± SD years	55.2 ± 13	55.4 ± 12.9	55 ± 13.6	NS
No. of men/women	17/153	15/123	2/30	NS
No. ANA negative/ACA positive/anti–topo I positive	7/77/60	7/77/34	0/0/26	<0.001
Disease duration, median (IQR) years	7.4 (3.2–12)	7.8 (3.1–12)	6.7 (3.5–15)	NS
MRSS, median (IQR)	4 (1–8)	3 (0–5)	14 (4–21)	<0.001
ILD, no. (%)	72 (42)	47 (34)	25 (78)	<0.001
FVC, mean ± SD % of predicted	102 ± 21	105 ± 19	90 ± 23	<0.001
DLco, mean ± SD % of predicted	76 ± 20	78 ± 19	67 ± 23	0.012
DLco/Va, mean ± SD % of predicted	79 ± 18	80 ± 17	74 ± 19	NS
Cochin Risk Prediction Score, mean ± SD	3.4 ± 0.9	3.3 ± 0.8	3.9 ± 1	0.001

* SSc = systemic sclerosis; lcSSc = limited cutaneous SSc; dcSSc = diffuse cutaneous SSc; NS = not significant; ANA = antinuclear antibody; ACA = anticentromere antibody; anti–topo I = anti–topoisomerase I; IQR = interquartile range; MRSS = modified Rodnan skin thickness score; ILD = interstitial lung disease; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; DLco/Va = DLco/alveolar volume.

was censored at the time of the last available clinical assessment. The Cox regression model was used for multivariate analysis of survival and to investigate hazard ratios (HRs). Besides raw data analysis, to increase the precision of our analyses, missing data on predictors were imputed using switching regression, an iterative multivariate regression technique that retains an element of random variation in the estimates (17). Using multiple imputation of predictors, 170 subjects were finally available for all the adjusted analyses. Two-sided *P* values less than 0.05 were considered significant.

RESULTS

Patient characteristics. Complete baseline and followup data were available for 170 patients. Table 1 shows demographic and clinical data according to the main disease subsets, limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc). Mean FVC and DLco were significantly lower in the patients with dcSSc ($P < 0.001$ and $P < 0.05$, respectively); this was probably due to the more frequent occurrence of ILD in this group ($P < 0.001$). DLco/Va values were similar in the 2 subsets (Table 1). Only FVC (odds ratio [OR] 0.96 [95% confidence interval 0.94–0.98], $P < 0.01$) and the presence of anti–topoisomerase I antibodies (OR 2.5 [95% confidence interval 1–6.3], $P < 0.05$) were independently associated with ILD in a model that also included age, cutaneous subset, and DLco.

The mean ± SD Cochin Risk Prediction Score in the whole sample was 3.4 ± 0.9, and it was significantly higher in patients with dcSSc. A total of 118 patients had a Cochin Risk Prediction Score above the cutoff of 2.73. Patients in the highest Cochin Risk Prediction Score quintile (n = 30) had scores of >4.18.

Clinical association of the stress echocardiographic response. Details of basal echocardiographic features and the response to stress exercise in these patients are reported elsewhere (12). The ergometric test revealed a significant increase of pulmonary artery systolic pressure under exercise in our SSc patients compared to basal values on standard echocardiography (mean ± SD 24 ± 8 mm Hg versus 36 ± 9 mm Hg; $P < 0.001$). Of the functional and SSc clinical variables analyzed in relation to the stress echocardiographic response, only ILD was associated with higher pulmonary artery systolic pressure and pulmonary artery systolic pressure under exercise, which is in accordance with findings of a previous study (12). There was a significant correlation between at-rest and post-exercise estimates (r = 0.9, $P < 0.01$). Consequently, for statistical analyses, pulmonary artery systolic pressure under exercise was corrected for basal pulmonary artery systolic pressure and expressed as the difference (Δpulmonary artery systolic pressure).

In a multivariate analysis that included variables such as interstitial involvement, age, disease duration, disease subset, autoantibody subgroups, and E′:A′ ratio <1 (for diastolic dysfunction) to assess major determinants of the stress echocardiographic response, Δpulmonary artery systolic pressure was significantly related only to the presence of ILD (adjusted coefficient 3.6, SE 1.35, $P < 0.01$). Δpulmonary artery systolic pressure values corrected for changes in CI during exercise (Δpulmonary artery systolic pressure/ΔCI) were higher in patients with dcSSc (median [IQR] mm Hg/liter/minute/m^2 5.6 [2.6–9.2], versus 3.4 [1.6–5.8] in patients with lcSSc; $P < 0.05$) and in those with ILD (median [IQR] mm Hg/liter/minute/m^2 5.1 [0–18.8], versus 2.9 [0–16] in those without ILD), but the corrected effect on the variable resulted in significance only for ILD (adjusted coefficient 1.8, SE 0.8, $P < 0.01$) when, again, a multivariate analysis included both inter-

Table 2. Features of the patients with ePASP <48 mm Hg and those with ePASP ≥48 mm Hg*

	ePASP <48 mm Hg (n = 149)	ePASP ≥48 mm Hg (n = 21)	*P*
Age, mean ± SD years	55.4 ± 13	54.1 ± 13.7	NS
No. of men/women	16/133	1/20	NS
No. with lcSSc/dcSSc	123/26	15/6	NS
No. ANA negative/ACA positive/anti–topo I positive	4/70/53	3/7/7	0.001
Disease duration, median (IQR) years	7.2 (3–12.3)	10 (6.7–18)	NS
MRSS, median (IQR)	6 (0–13)	3 (0–5)	NS
ILD, no. (%)	59 (39)	13 (62)	NS
FVC, mean ± SD % of predicted	103 ± 21	96 ± 21	NS
DLco, mean ± SD % of predicted	76 ± 20	75 ± 21	NS
DLco/VA, mean ± SD % of predicted	78 ± 17	87 ± 17	NS
Cochin Risk Prediction Score, mean ± SD	3.4 ± 0.9	3.2 ± 0.8	NS
ΔPASP, mean ± SD mm Hg	8.27 ± 5.6	20 ± 5.2	<0.001
ΔPASP/ΔCI, median (IQR) mm Hg/liter/minute/m^2	3.1 (1.6–5.5)	8.5 (5.8–10.7)	<0.001

* ePASP = pulmonary artery systolic pressure under exercise; ΔPASP = ePASP − PASP; ΔCI = change in cardiac index (see Table 1 for other definitions).

stitial lung and skin involvement to predict Δpulmonary artery systolic pressure/ΔCI values.

SSc patients were divided into 2 groups: those with a pulmonary artery systolic pressure under exercise value below the previously defined cutoff of 48 mm Hg (group 1; n = 149) and those with a value at or above the cutoff (group 2; n = 21). Patients in the 2 groups did not differ in terms of sex or SSc subset. Anticentromere antibodies were more frequent in group 1 (Table 2), but this association was no longer relevant when adjusted for cutaneous involvement (not shown). Similarly, there was no statistically significant difference in age, disease duration, modified Rodnan skin thickness score (MRSS) (18), FVC (% of predicted value), DLco (% of predicted value), or DLco/VA (% of predicted value) in the univariate analysis (Table 2). The mean Cochin Risk Prediction Score also did not differ between the 2 groups. The presence of ILD tended to be more frequent in the group with pulmonary artery systolic pressure under exercise ≥48 mm Hg than in the group with a lower pulmonary artery systolic pressure under exercise (62% versus 39%; $P = 0.053$). ILD was again significantly predictive of pulmonary artery systolic pressure under exercise of ≥48 mm Hg (OR 10 [95% confidence interval 1.4–70.4], $P < 0.05$) in a multivariate logistic regression analysis with correction for the effect of disease subset, age, sex, disease duration, DLco (% of predicted value), E′:A′ ratio, and autoantibody status.

PH development during followup. During a mean ± SD followup of 3.5 ± 0.2 years, 9 patients were referred for RHC, 5 in group 1 and 4 in group 2 (3.4% versus 19%; $P < 0.01$). Mean ± SD pulmonary

Table 3. Baseline features of the patients with complete followup who did not develop PH and those who did develop PH*

	SSc without features of PH (n = 164)	SSc with PH (n = 6)	*P*
Age, mean ± SD years	55 ± 13	59 ± 13	NS
No. of men/women	17/147	0/6	NS
No. with lcSSc/dcSSc	132/32	6/0	NS
No. ANA negative/ACA positive/anti–topo I positive	7/73/58	0/4/2	NS
Disease duration, median (IQR) years	7.3 (3–12)	10 (7–11.5)	NS
ILD, no. (%)	95 (58)	3 (50)	NS
FVC, mean ± SD % of predicted	102 ± 21	107 ± 24	NS
DLco, mean ± SD % of predicted	77 ± 19	53 ± 24	<0.01
DLco/VA, mean ± SD % of predicted	80 ± 17	62 ± 15	<0.05
Cochin Risk Prediction Score, mean ± SD	3.4 ± 0.9	4.2 ± 0.9	<0.05
PASP, mean ± SD mm Hg	23.7 ± 8.1	29.5 ± 5.5	NS
ePASP, mean ± SD mm Hg	33.1 ± 12.6	47.7 ± 12.2	<0.01
ΔPASP, mean ± SD mm Hg	9.4 ± 6.5	18.2 ± 7	<0.001
ΔPASP/ΔCI, median (IQR) mm Hg/liter/minute/m^2	3.5 (1.7–5.9)	10.9 (3.2–15.5)	<0.05

* PH = pulmonary hypertension; PASP = pulmonary artery systolic pressure; ePASP = PASP under exercise; ΔPASP = ePASP − PASP; ΔCI = change in cardiac index (see Table 1 for other definitions).

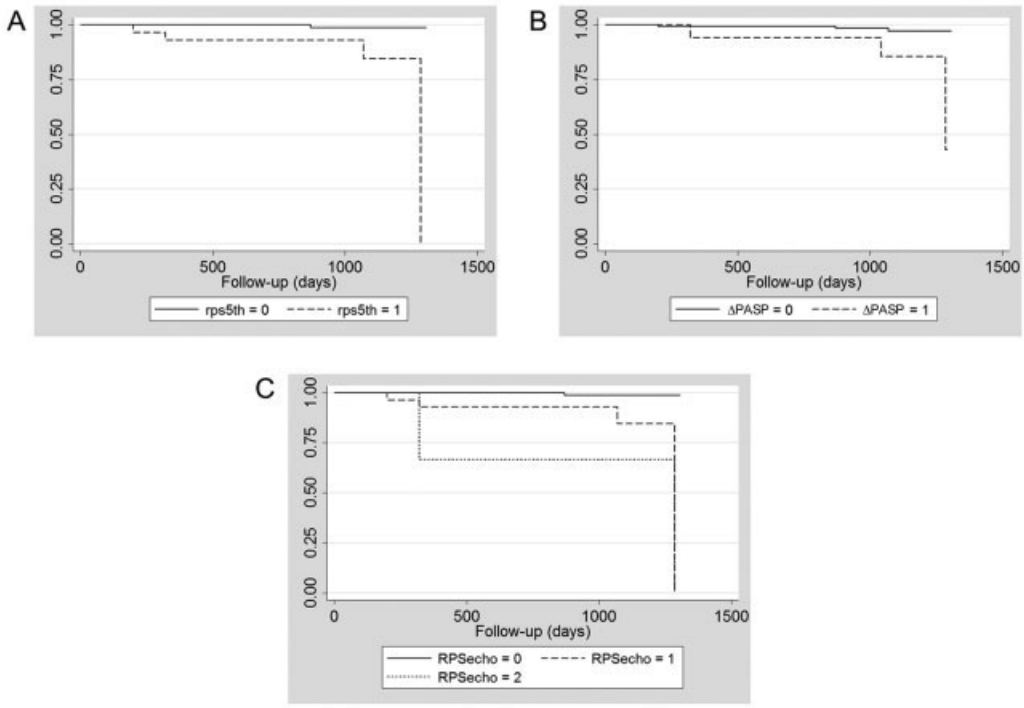

Figure 1. Univariate survival curves (representing survival without development of pulmonary hypertension) according to whether the Cochin Risk Prediction Score (rps5th) was or was not in the fifth quintile (0 = no, 1 = yes) (**A**) or according to the change in pulmonary artery systolic pressure (ΔPASP), equal to PASP under exercise − PASP (0 = ≤18 mm Hg, 1 = >18 mm Hg) (**B**), and for different combinations of the 2 parameters (RPSecho) (0 = neither parameter present, 1 = either parameter present, 2 = both parameters present) (**C**).

artery systolic pressure measured by standard echocardiography was significantly higher and mean ± SD DLco and DLco/VA were significantly lower in these patients than in those not undergoing RHC (43 ± 7 mm Hg versus 21 ± 11 mm Hg; $P < 0.01$ and 62 ± 27% of predicted value versus 77 ± 19% of predicted value; $P < 0.05$ and 65 ± 16% of predicted value versus 80 ± 17% of predicted value; $P < 0.01$, respectively), while FVC or the Cochin Risk Prediction Score did not differ between groups. Overall, 6 of 170 patients (3.5%) developed PH as defined by a mean PAP of ≥25 mm Hg. Group 1 PAH was confirmed in 3 patients, 1 patient had group 3 precapillary PH, and in 2 patients PH was due to left heart disease (group 2) (1). The main clinical features of these patients at baseline are detailed in Table 3. Mean DLco or DLco/VA, Cochin Risk Prediction Score, pulmonary artery systolic pressure under exercise, Δpulmonary artery systolic pressure, and Δpulmonary artery systolic pressure/ΔCI measured upon study enrollment differed significantly between patients who

Table 4. HRs (univariate, adjusted, and with multiple imputation adjustment) for PH development during followup*

Variable	Univariate HR (95% CI) (n = 170)	*P*	Adjusted HR (95% CI) (n = 152)	*P*	Multiple imputation adjusted HR (95% CI) (n = 170)	*P*
ΔPASP (5 mm Hg increase)†	2.4 (1.2–4.8)	0.010	3.4 (1.4–8)	0.007	3.1 (1.4–7)	0.006
ΔPASP/ΔCI†	1.3 (1.1–1.5)	0.002	1.3 (1.04–1.6)	0.018	1.3 (1.05–1.6)	0.015
Cochin Risk Prediction Score, fifth quintile‡	9.5 (1.7–52.4)	0.010	9.3 (1.4–63.7)	0.022	9.9 (1.4–70.5)	0.022
ePASP ≥48 mm Hg†	6 (1.2–30)	0.030	12 (0.7–223)	NS	6.5 (0.5–77.9)	NS

* HR = hazard ratio; 95% CI = 95% confidence interval; NS = not significant (see Table 3 for other definitions).
† Adjusted for presence of interstitial lung disease, autoantibody status, ratio of left ventricular peak early:peak late diastolic velocities, or fifth quintile of Cochin Risk Prediction Score (yes or no).
‡ Adjusted for ΔPASP (5 mm Hg increase).

subsequently developed PH and patients who were free of this complication at the end of followup (Table 3); notably, however, basal pulmonary artery systolic pressure values did not distinguish between patients with and those without PH at the end of followup.

PH developed in a significantly higher proportion of patients in the fifth quintile of Cochin Risk Prediction Score (13% of patients, versus 2% in the other quintile groups; $P < 0.05$). Notably, a Cochin Risk Prediction Score of >2.73 did not predict PH (4% of patients with a Cochin Risk Prediction Score of >2.73 developed PH, versus 3% of patients with a Cochin Risk Prediction Score of ≤2.73; $P = 1$). At the time of RHC referral or at the last followup visit, DLCO was significantly lower in patients with PH than in those without (mean ± SD 55.8 ± 11.7% of predicted value versus 72.9 ± 18.2% of predicted value; $P < 0.05$); although the difference did not reach statistical significance, DLCO/VA was also lower in PH patients (67.7 ± 16.2% of predicted value versus 78.6 ± 17% of predicted value) (further information is available upon request from the corresponding author). Kaplan-Meier curves revealed poorer PH-free survival in patients in the fifth quintile of Cochin Risk Prediction Score ($P < 0.01$) (Figure 1A). PH developed more frequently in patients with pulmonary artery systolic pressure under exercise of ≥48 mm Hg on stress echocardiography (14% of patients, versus 2% of patients with pulmonary artery systolic pressure under exercise <48 mm Hg; $P < 0.05$) and was associated with increased Δpulmonary artery systolic pressure or Δpulmonary artery systolic pressure/ΔCI values.

Multivariate Cox regression analysis showed that an increase in these echocardiographic estimates and inclusion in the highest quintile of Cochin Risk Prediction Score significantly predicted PH-free survival and were the only parameters associated with a significant and independent fold increase in HR for the development of PH after adjustment for potential confounders (the presence of ILD, autoantibody status, and E′:A′ ratio) (Table 4). In particular, after adjustment for other confounders, pulmonary artery systolic pressure under exercise ≥48 mm Hg did not retain its association with PH development, whereas both Δpulmonary artery systolic pressure (or Δpulmonary artery systolic pressure/ΔCI) and being in the fifth quintile of Cochin Risk Prediction Score showed significant HRs for PH.

Based on these results, we carried out an ROC curve analysis to identify the Δpulmonary artery systolic pressure value that could identify patients with an increased risk of PH during followup. The ROC curve for Δpulmonary artery systolic pressure (Figure 2) showed that a cutoff of >18 mm Hg had a sensitivity of 50% and a specificity of 90% in identifying patients who subsequently developed PH (AUC 0.82 [95% confidence interval 0.7–0.95], $P < 0.01$). Upon enrollment in the study, 19 patients (11%) had Δpulmonary artery systolic pressure >18 mm Hg. No association with any other rheumatologic clinical feature (ILD, disease subset, E′:A′ ratio, etc.) was demonstrated in this group of patients. The mean ± SD Cochin Risk Prediction Score in these patients was 3.33 ± 0.83, versus 3.39 ± 0.9 in the rest of the population ($P = 0.3$). The majority of them (84%) had Cochin Risk Prediction Score values below the fifth quintile. The percentage of patients with PH upon completion of followup was significantly higher in the group with Δpulmonary artery systolic pressure >18 mm Hg (16% versus 2%; $P < 0.05$). PH-free survival curves were worse in patients with Δpulmonary artery systolic pressure >18 mm Hg ($P < 0.05$) or with the combination of this condition and having a Cochin Risk Prediction Score in the fifth quintile (Figures 1B and C).

In detail, in our PH case series, 2 of 6 patients (33%; 1 with PAH, 1 with group 3 PH) both had Cochin Risk Prediction Scores in the fifth quintile and showed Δpulmonary artery systolic pressure >18 mm Hg during stress echocardiography. Two of 6 patients (33%; 1 with PAH, 1 with group 2 PH) only had Cochin Risk Prediction Scores in the fifth quintile. One of 6 patients (17%; with group 2 PH) only had Δpulmonary artery systolic

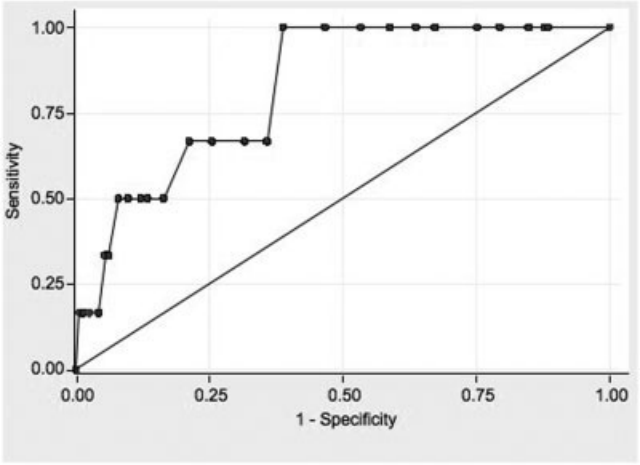

Figure 2. Receiver operating characteristic curve for the level of change in pulmonary artery systolic pressure (ΔPASP), equal to PASP under exercise − PASP, that would best predict development of pulmonary hypertension (area under the curve [AUC] 0.82 [95% confidence interval 0.7–0.95], $P < 0.01$). Diagonal line indicates AUC = 0.5.

pressure >18 mm Hg. Finally, 1 patient (17%; with PAH) was not identified by either feature.

DISCUSSION

Thus far, the role of stress echocardiography in predicting PH in SSc patients has been investigated only in cross-sectional studies. Steen et al (10) evaluated whether exercise echocardiography could identify patients who might have PH in an SSc patient population with symptoms suggesting that they were at risk for PH. Those authors found that during exercise, 17 of 21 patients (81%) with an increase in pulmonary artery systolic pressure under exercise of >20 mm Hg from resting values (pulmonary artery systolic pressure) had PH confirmed by RHC. However, in only 4 of these 17 patients (19% of the total of 21 patients) was the mean PAP ≥25 mm Hg at rest, whereas the other patients fulfilled the definition of exercise PH of a mean PAP of >30 mm Hg after exercise; the use of this definition is not supported by current evidence-based guidelines (1). In their cross-sectional multicenter study, Grünig et al (11) investigated the potential of stress echocardiography to identify hypertensive responses to exercise or hypoxia in relatives of patients with idiopathic or familial PAH. They found that more relatives with idiopathic or familial PAH than healthy controls had a VTR of >3.08 meters/second (which corresponds to an estimated pulmonary artery systolic pressure of >43 mm Hg), and that relatives had significantly higher mean pulmonary artery systolic pressure under exercise or Δpulmonary artery systolic pressure (mean ± SD 39.5 ± 5.6 mm Hg versus 35.5 ± 5.4 mm Hg and 18.8 ± 10.6 mm Hg versus 15.2 ± 7.1 mm Hg, respectively) (11).

The present study is the first longitudinal study to investigate the role of basal stress echocardiography in predicting the development of PH in SSc outpatients in NYHA class I or II without clinically suspected PH at baseline and with pulmonary artery systolic pressure within normal limits. We previously reported that SSc patients had significantly higher estimated pulmonary artery systolic pressures under exercise than did healthy controls and that values were higher in patients with ILD and/or LV filling abnormalities (12). In the present study we slightly modified the definition of ILD in our cohort in order to better ascertain the influence of even small interstitial changes on the development of hypertensive changes of the pulmonary vasculature. We confirmed the previous finding of an association of ILD with higher stress pulmonary artery responses at the baseline evaluation. ILD is thus an important variable, which we included in the PH survival model. In the first study (12), we also identified a subset of patients who reacted to exercise stress with a very high pulmonary artery systolic pressure (≥48 mm Hg). Longitudinal study of our cohort revealed that, by univariate analysis, PH-free survival was lower in patients with pulmonary artery systolic pressure under exercise of ≥48 mm Hg.

Multivariate analysis of the followup data showed that the difference versus basal values of estimated pressures (Δpulmonary artery systolic pressure) rather than the absolute pulmonary artery systolic pressure under exercise or pulmonary artery systolic pressure under exercise ≥48 mm Hg was predictive of the development of PH. Indeed, mm Hg increases in Δpulmonary artery systolic pressure conferred a significantly higher risk of PH development independent of other clinical predictors, such as ILD. Importantly, this was also true when Δpulmonary artery systolic pressure was related to CI changes during exercise, in the attempt to correct the rise in pressure for adjustments of the vascular reserve, a ratio that is clearly unbalanced in SSc (12).

In an ROC curve analysis, we found that Δpulmonary artery systolic pressure increase and values >18 mm Hg were highly specific for PH development in our cohort. Notably, this value is consistent with those indicating a positive stress echocardiography test result (15 or 20 mm Hg) in previous cross-sectional studies that also focused on the pulmonary artery systolic pressure changes during exercise rather than on their absolute value under stress (10,11,19,20). Despite the fact that the AUC of the ROC curve was significant, the sensitivity of our cutoff was rather low (50%), and this represents a limitation of our analysis. Moreover, it should be taken into account that there could be some misclassification bias in our study given that, for ethical and economic reasons, RHC was not systematically performed on all patients, but rather was performed only if recommended by clinicians who were blinded with regard to exercise echocardiography findings. Without RHC data on all patients one cannot formally exclude the possibility that in some patients, PH, though first detected during followup and recorded as incident, may have in fact been present prior to study enrollment. However, the study was designed to assess the predictive value of stress echocardiography results in a real-life SSc cohort screened for PH according to standard recommendations (4). In addition, exercise echocardiography was not repeated longitudinally during followup. Future studies might clarify which Δpulmonary artery systolic pressure values should be used to interpret exercise test results and define indica-

tions and cost-effectiveness for performing exercise testing in SSc.

From a pathophysiologic viewpoint, both pulmonary artery systolic pressure under exercise and the Δpulmonary artery systolic pressure:ΔCI ratio probably depend mainly on the inability of the SSc pulmonary vascular bed to dilate under exercise and consequently would reflect the peculiar stiff vascular system characteristic of SSc (21). From a clinical point of view, our data suggest that this inability, when exceeding a defined value, is predictive of PH during followup.

The outcome predictive measure we identified did not distinguish between PH groups due to the low numbers of events that were observed in the relatively short followup period, and this may be another limitation of the study. The recently described Cochin Risk Prediction Score for PH, based on simple clinical features (age, DL_{CO}/V_A, and FVC) (13), was proposed and validated for all PH groups combined, as a single outcome.

The absolute Cochin Risk Prediction Score values in our cohort were somewhat higher than in the patients described by Meune et al, with a mean value that was well above their cutoff for PH (2.73) and comparable to that in high-risk patients (mean ± SD 3.57 ± 0.45) in the original derivation cohort (13). This discrepancy limits the application of Cochin Risk Prediction Score absolute values and might be due to the fact that, although we excluded subjects who already had features known to predict PH risk, our study was conducted in only 2 referral centers from a single country. Nevertheless, by calculating specific cutoffs based on the variable distribution and distinguishing patients in the fifth quintile of Cochin Risk Prediction Score, as also done by Meune and coworkers (13), our longitudinal analysis confirmed that this feature was significantly associated with development of PH. Moreover, the univariate cumulative 3-year survival rates we observed were strikingly similar to those obtained by Meune et al (13), which, in both studies, were significantly worse in the subgroup of patients in the fifth quintile of the Cochin Risk Prediction Score.

In this respect, exercise echocardiography contributed to the prediction of PH development independent of classification by Cochin Risk Prediction Score. In fact, the majority of patients (84%) identified by the 18 mm Hg cutoff in the test were not in the fifth quintile of the Cochin Risk Prediction Score distribution, providing an additional tool to identify SSc patients at risk of otherwise unsuspected PH. Accordingly, in our multivariate analysis of PH-free survival, Δpulmonary artery systolic pressure and Cochin Risk Prediction Score in the fifth quintile conferred significant and independent risks of PH that even worsened PH survival curves when present together. Nonetheless, while our findings support the significant contribution of the Cochin Risk Prediction Score in PH risk stratification, our study is limited by a relatively short followup period as mentioned above, and highlights the need for further investigation to identify absolute values to facilitate the application of the Cochin Risk Prediction Score in daily clinical practice.

A further limitation of the present study is that Doppler echocardiography and tissue Doppler imaging at rest and particularly after exercise are critically operator dependent and therefore should be performed by dedicated and expert cardiologists in referral centers, and this may not be accessible to every patient with SSc. In any event, PH is a common finding in SSc (22), and given the complexity of this pathophysiologic condition and its various etiologies, expert management is recommended to obtain a proper diagnosis and eventual therapy in a relatively early phase of the clinical picture.

Recently, after our manuscript was submitted, Kovacs et al pointed out that 10 patients with a marked baseline exercise-induced increase in PAP experienced a significant increase in mean PAP (evaluated by RHC), both at rest and during exercise, over 1 year and that such changes were attenuated by a subsequent 6-month treatment with bosentan (23). Our results would question the usefulness of PAH therapy for each SSc patient with a marked baseline exercise-induced increase in PAP. Actually, of our 6 patients who developed PH during followup, 1 presented with PAH associated with ILD, in which this drug is not recommended, and 2 developed PH secondary to left heart involvement, in which this drug is contraindicated (1).

In conclusion, we found that PH during followup is significantly associated with Δpulmonary artery systolic pressure (or with Δpulmonary artery systolic pressure/ΔCI) and with a Cochin Risk Prediction Score within the highest quintile of values detected in our SSc patients, and that a Δpulmonary artery systolic pressure of >18 mm Hg is significantly associated with the development of PH during followup. Herein we demonstrate that, given its independent effect in the longitudinal detection of PH in SSc patients, the Doppler echocardiographic exercise test can effectively complement clinical observations. Consequently, stress Doppler echocardiography might have a role in augmenting the efficacy of screening algorithms and detection programs

(24) identifying a group at increased risk of developing PH.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Montecucco had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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